Unrepresentativeness

Although it is clear that the combined study population in Table 1 is not fully representative of non-smokers, this does not appear to be a serious issue, since studies have been carried out in the US, UK, Greece, Sweden, Japan and Hong Kong, and Wald et al. (1986) found no evidence of significant heterogeneity of relative risk estimates.

Sample Size

While none of the studies considered in Table 1 concern particularly large numbers of non-smokers with lung cancer, chance can hardly be the total explanation of the association between passive smoking and lung cancer since the overall relative risk estimate quoted by Wald et al. (1986) of 1.35 is quite highly statistically significant, with 95% confidence limits of 1.19–1.54.

Confounding

Not all the studies considered have taken into account the possible confounding effect of factors known or suspected to be related to lung cancer, such as occupation or nutrition. Although it would perhaps be expected that non-smokers married to smokers might to some extent share the tendency of smokers to work in dirtier jobs, standardisation for occupation, or indeed any confounding factor, has never been found in practice to explain any material part of the association between lung cancer and passive smoking. It does not seem likely that failure to take confounding factors into account has materially affected the issue.

Inappropriate Choice of Controls

General scientific principles demand that like should be compared with like as far as possible. In a number of studies, there were clear exceptions to this. One example is the study of Trichopoulos et al. (1981, 1984) in which controls came from a different hospital. This may cause bias if patients came from different catchment areas with different smoking characteristics. Another example is the recently reported study of Humble et al. (1987), in which virtually all the interviews with controls were conducted directly while much of the data for cases came from surrogates. While inappropriate choice of controls may have materially biassed a few studies, it does not seem very likely, however, that it is a major explanation for the huge discrepancy.

Inaccuracy of Disease Classification

It is well known that diagnosis of lung cancer is imperfect and studies such as those by Garfinkel et al. (1985) which took pains to check and review all available evidence are to be preferred to those that did not do so. However, random misclassification of diagnosis would be expected to reduce the observed association between lung cancer and passive smoking, not increase it, and differential misclassification of diagnosis does not seem very likely, inasmuch as the doctor making the diagnosis is likely to have been blind to the

2023381516

patient's ETS exposure in most cases, and not to have been affected by it even if he was, given most diagnoses were made before the first study on the issue was published in 1981.

Non-reporting Bias

A problem in combining results from various studies to come to an overall assessment of the evidence, by so-called "meta-analysis", is the possibility that the studies being combined are not representative of all those that have been carried out. In particular, overall estimates of relative risk may be biassed upward if a scientist is less likely to submit for publication, or a journal is less likely to publish, studies which show no significant relationship of disease to the factor of interest or a significant trend in the direction opposite to that expected in advance. Convincing evidence of bias resulting from this in the context of randomised controlled trials has recently been collected by Chalmers et al. (1987) and the problem may generally be greater in epidemiological studies. One can easily imagine an investigator running a range of statistical analyses, finding a few significant associations of interest, and then publishing papers on those, ignoring the non-significant relationships. One can also imagine journals not being too keen to given space to a paper on a new null association and one must inevitably wonder whether the reason the first two studies published on passive smoking and lung cancer (Hirayama 1981; Trichopoulos 1981) found a significant association was because first published papers on any association tend to be positive. Indeed, there seems a case for carrying out meta-analysis giving most weight to studies showing no association and least weight to studies published first.

Although it is obviously important to conduct research into the problems of non-reporting bias in epidemiological studies, it is difficult to claim that it is the full explanation of the overall association between passive smoking and lung cancer. The reasons for this view are two-fold. Firstly, the overall association remains significant (though the relative risk estimate reduces to 1.20), even after eliminating the Hirayama and Trichopoulos results. Secondly, the fact that lung cancer and passive smoking has been a very "hot" issue in recent years suggests researchers should now be able to publish results from studies showing no association between passive smoking and lung cancer risk.

Lack of Objective Measure of ETS Exposure

A limitation of all the published epidemiological evidence is lack of objective measurement of exposure to ETS. Subjects are classified mainly by whether or not they are married to a smoker and occasionally by reported degree of exposure outside the home, but there are no data available either on ambient levels of tobacco smoke constituents at home or at work or on levels in body fluids such as blood, urine or saliva. While (e.g. see Table 3) it can be shown that marriage to a smoker is indeed associated with increased levels of cotinine, the relatively crude method used for determining exposure leads to possibilities of bias in case-control studies where knowledge of disease may consciously or subconsciously affect reporting of ETS exposure. While this may have caused upward bias of the reported relative risk in some case-control studies, it can hardly explain the whole association, since it would not be expected to cause upward bias in prospective studies and the association seems as strong in prospective as in case-control studies.

Source: https://www.industrydocuments.ucsf.edu/docs/kznx0000

Table 5. Hypothetical example of bias due to misclassification of 5% of smoking subjects as non-smokers

Smoking habit*		Assumed		Observed			
Subject	Spouse	N	Risk	N	Risk	Passive effect	Active effect
NS	NS	60	1	60 + 2 = 62	1.61	1	
NS	S	40	1	40 + 3 = 43	2.33	1.44	
NS	Total	100	1	100 + 5 = 105	1.90		1
S	NS	40	20	40 − 2 = 38	20		
S	S	60	20	60 − 3 = 57	20		
NS	Total	100	20	100 − 5 = 95	10		10.5

Assumed concordance = (60 × 60)/(40 × 40) = 2.25
Observed concordance = (62 × 57)/(43 × 38) = 2.16

* NS, non-smoker; S, smoker

Lack of Objective Measure of Active Smoking Status

Although considered last, this appears to be the most serious problem affecting the epidemiological evidence on passive smoking and lung cancer. As will be shown in the next section, completely erroneous conclusions can be reached when the "non-smokers" being studied actually include a small proportion of misclassified true smokers.

Misclassification of Active Smoking Habits as a Major Source of Bias

As shown in Table 5, misclassification of a small proportion of smokers as non-smokers, coupled with a tendency for smokers to be married to smokers ("concordance") can create an apparent positive effect of passive smoking when no actual effect exists. It also leads to an underestimation of the active smoking effect and of the concordance. The passive smoking bias depends critically on the assumed relative risk for active smoking, the degree of concordance and on the level of misclassification of subject smokers as non-smokers. This source of bias will also produce an artificial dose response relationship when the "non-smoking" subjects are divided according to the amount smoked by the spouse. It can be shown (Lee 1988b) that misclassification of non-smoking subjects as smokers and of smoking spouses as non-smokers causes a degree of bias that is minor compared with that resulting from misclassification of smoking subjects as non-smokers.

In an attempt to determine the extent to which smokers misreported their smoking habits and to which smokers tend to be married to smokers, Lee (1987) carried out three separate studies. In the first study, which concerned accuracy of reported current habits, 1775 British subjects were asked about their smoking habits and use of other nicotine products in a non-health context likely to minimize underreporting of smoking. They were then (with no prior warning) asked to provide saliva for cotinine analysis and 1537 agreed to do so. As shown in Table 3 there was in general a very marked difference between the cotinine levels of tobacco users and non-users. Using 30 ng/ml as a cut-off,

2023381519

1.1% of self-reported non-users could be classified as occasional users, with levels of to 100 ng/ml, while 1.4% could be classified regular users, with levels above 100 ng/ml.

The second study, which aimed at obtaining information, on accuracy of past smoking habits, followed up in 1985 540 subjects previously interviewed in 1980 about their smoking habits. Ten% claiming on one occasion never to have smoked made inconsistent statements on the other occasion, with inconsistent smokers being more often men, old, smokers of fewer cigarettes and long term ex-smokers.

The third study, which aimed at obtaining information on smoking habit concordance, involved 8857 subjects aged 16+ interviewed regarding their own smoking habits and that of their spouse. The concordance ratio, 3.55 in men and 3.07 in women, was found to be rather greater than that assumed in the example in Table 5. Concordance rose with amount smoked. Thus, the chance of having a spouse who was a manufactured cigarette smoker was 22% for subjects who reported no such smoking, and 45%, 52% and 59% respectively for subjects who reported smoking 1–17, 18–22 and 23+ manufactured cigarettes per day.

From the data obtained, Lee (1987) concluded that misclassification could bias relative risk estimates in relation to passive smoking upwards by a factor of 1.31 in men and 1.24 in women, not significantly different from the pooled estimate of risk in relation to passive smoke exposure.

At about the same time as Lee presented his findings, Wald et al. (1986) used similar techniques to estimate the bias from misclassification, but based on a number of smaller, and less representative studies, not specifically designed for the purpose. They estimated this misclassification would have less effect, reducing the pooled estimate of risk only from 1.35 to 1.30, i.e. it had only caused upward bias by a factor of 1.04.

Examination of the detail of how the estimates of bias of Wald et al (1986) and of Lee (1987) were arrived at reveals three reasons for the difference. The first was that Wald et al. (1986) used an assumed relative risk of 8 for the effect of active smoking observed in women whereas Lee (1987) used 10. The second was that the calculations of bias by Wald et al. (1986) were mathematically inaccurate, due to confusion between true relative risks in relation to active smoking and those observed (which are affected by misclassification). These are less important than the third reason, which is that Lee et al. (1987) found that 1.4% (10/808) self-reported non-smokers were current regular smokers, whereas Wald et al. (1986) only found 0.14% (1/705) such cases.

In an attempt to reconcile this difference, I have recently conducted a detailed literature review of the evidence on misclassification of smoking habits, which will be published as a book early in 1988.

Despite the various study designs and populations involved a number of clear conclusions were reached:

(1) Even in circumstances that are apparently similar quite a wide variation in the extent of misclassification can be found.
(2) The proportion of "non-smokers" subsequently found actually to be smokers is markedly higher in smoking cessation studies than in studies where the respondent is under no special pressure not to smoke.
(3) The proportion of "non-smokers" subsequently found actually to be smokers is also markedly higher in lung cancer patients than in the general population. This is not surprising in view of the overall *a priori* expectation that a lung cancer patient actually is a smoker.
(4) Studies of "non-smokers" without lung cancer and under no special pressure not to smoke suggest that around 4% are likely actually to be current smokers. While not all

Source: https://www.industrydocuments.ucsf.edu/docs/kznx0000

studies provide information on the extent to which such misclassified smokers smoke, and those that do indicate many of them are occasional smokers, it seems that 1 to 2% of self-reported non-smokers are regular smokers.

(5) In addition to these misclassified current smokers there are a somewhat larger number of ex-smokers misclassified as never smokers. Available information suggests that these tend to have smoked less and a longer time ago than average ex-smokers.

(6) None of the studies have investigated whether the extent to which smokers deny smoking depends on whether their spouse happens to smoke, which is of theoretical importance as it could materially affect estimates of bias.

(7) There is even now virtually no information on the extent to which smoking habits might be misclassified in Japan and Greece, from whence came the early epidemiological evidence on passive smoking and lung cancer. The only study in Japan, by Akiba et al. (1986), provided data suggestive of substantial misclassification of smoking habits. Here, of 187 men who reported not smoking in 1964–68, as many as 96 (51%) reported in 1982 that they had smoked.

While there is an obvious need for further research on misclassification of smoking habits the results of the review[1] suggested strongly that Wald et al. (1986) had seriously underestimated its importance.

Overall Conclusion

It has clearly been shown that there is a huge discrepancy between the relative doses of smoke constituents to which passive and active smokers are exposed and the much larger relative effect claimed from epidemiological evidence. The most likely explanation for this discrepancy seems to be a persistent bias affecting all the studies due to a small proportion of smokers being wrongly classified as non-smokers in the epidemiological studies.

References

Adlkofer F, Scherer G, von Hees U (1985) Passive smoking. N Engl J Med 312:719–720

Akiba S, Kato H, Blot WJ (1986) Passive smoking and lung cancer among Japanese women. Cancer Research 46:4804–4807

Alderson MR (1983) An introduction to epidemiology. Macmillan

Alderson MR, Lee PN, Wang R (1985) Risks of lung cancer, chronic bronchitis, ischaemic heart disease and stroke in relation to type of cigarette smoked. J Epidemiology and Community Health 39:286–293

Arundel A, Irwin T, Sterling TK, Weinkam J (1986) Nonsmoker lung cancer risks from exposure to tobacco smoke particulates. Stated to be available on request in: Arundel A, Irwin T, Sterling T. Nonsmoker lung cancer risks from tobacco smoke exposure: An evaluation of repace and lowrey's phenomenological model. J Environmental Science and Health Part C 4:93–118

Buffler PA, Pickle LW, Mason TJ, Contant C (1984) The causes of lung cancer in Texas. In: Lung cancer causes and prevention. Chemie International Inc, pp 83–99

[1] Supported by a recent large study by Coultas et al. (American Review of Respiratory Diseases, 1987, 136, 305–309) who found 63 subjects with salivary cotinine >20 ng/ml among a sample of 1,360 New Mexicans reporting they were not current smokers.

2023815 18

Chalmers TC, Levin H, Sachs HS, Reitman D, Berrier J, Nagalingam R (1987) Meta-analysis of clinical trials as a scientific discipline. I: Control of bias and comparison with large cooperative trials. Statistics in Medicine 6:315–325

Chan WC, Fung SC (1982) Lung cancer in non-smokers in Hong Kong. Cancer campaign. In: Cancer epidemiology. Fischer, vol 6, 199–202

Correa P, Pickle LW, Fontham E, Lin Y, Haenszel W (1983) Passive smoking and lung cancer. Lancet 2:595–597

Dalager NA, Pickle LW, Mason TJ, et al (1986) Relation of passive smoking to lung cancer. Cancer Research 46:4808–4811

Doll R (1986) Lung cancer observed and expected changes in incidence from active and passive smoking. XIV UICC Conference, Budapest

Doll R, Peto R (1978) Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. J Epidemiology and Community Health 32:303–313

Garfinkel L (1981) Time trends in lung cancer mortality among non-smokers and a note on passive smoking. J National Cancer Institute 66:1061–1066

Garfinkel L, Auerbach O, Joubert L (1985) Involuntary smoking and lung cancer: A case-control study. J National Cancer Institute 75:463–469

Gillis CR, Hole DJ, Hawthorne V, Boyle P (1984) The effect of environmental tobacco smoke in two urban communities in the west of Scotland. Eur J Resp Dis [Suppl 133] 65:121–126

Hiller FC, Mazumder MK, Wilson JD, McLeod PC, Bone RC (1982a) Human respiratory tract deposition using multimodal aerosols. J Aerosol Science 13:337–343

Hiller FC, McCusker KT, Mazumder MK, Wilson JD, Bone RC (1982b) Deposition of sidestream cigarette smoke in the human respiratory tract. American Review of Respiratory Diseases 125:406–408

Hirayama T (1981) Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. Br Med J 282:183–185

Hirayama T (1984) Cancer mortality in non-smoking women with smoking husbands in a large-scale cohort study in Japan. Preventive Medicine 13:680–690

Humble CG, Samet JM, Pathak DR (1987) Marriage to a smoker and lung cancer risk. Am J Public Health 77:598–602

Jarvis M, Tunstall-Pedoe H, Feyerabend C, Vesey C, Salloojee Y (1984) Biochemical markers of smoke absorption and self-reported exposure to passive smoking. J Epidemiology and Community Health 38:335–339

Kabat GC, Wynder EL (1984) Lung cancer in nonsmokers. Cancer 53:1214–1221

Koo LC, Ho JH-C, Saw D (1984) Is passive smoking an added risk factor for lung cancer in Chinese women? J Experimental and Clinical Cancer Research 3:277–283

Koo LC, Ho JH-C, Saw D, Ho C-Y (1987) Measurements of passive smoking and estimates of lung cancer risk among non-smoking Chinese females. Int J Cancer 39:162–169

Lee PN (1984) Passive smoking. In: Cumming G, Bonsignore G (eds) Smoking and the lung. Plenum Publishing Corporation, p 216

Lee PN (1987) Passive smoking and lung cancer association: A result of bias? Human Toxicology 6

Lee PN (1988a) Difficulties in studying weak associations epidemiologically with particular reference to environmental tobacco smoke exposure and lung cancer (submitted for publication)

Lee PN (1988b) Passive smoking and lung cancer. Association on artefact due to misclassification of smoking habits. Springer (in press)

Lee PN, Chamberlain J, Alderson MR (1986) Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. Br J Cancer 54:97–105

Matsukura S, Taminato T, Kitano Y, et al (1984) Effects of environmental tobacco smoke on urinary cotinine excretion in nonsmokers. N Engl J Med 311:828–832

Pershagen T, Hrubec Z, Svensson C (1987) Passive smoking and lung cancer in Swedish women. Am J Epidemiology 125:17–24

Pittenger DJ (1985) Passive smoking. N Engl J Med 312:720

Source: https://www.industrydocuments.ucsf.edu/docs/kznx0000

Robins J (1986) Risk assessments – exposure to environmental tobacco smoke and lung cancer. Appendix D to environmental tobacco smoke. Measuring exposure and assessing health effects. Committee on passive smoking. Board on environmental studies and toxicology, pp 294–336, Washington, DC. National Research Council. National Academy Press

Trichopoulos D, Kalandidi A, Sparros L, Macmahon B (1981) Lung cancer and passive smoking. Int J Cancer 27:1–4

Trichopoulos D, Kalandidi A, Sparros L (1983) Lung cancer and passive smoking: Conclusion of Greek study. Lancet 2:677–678

Wald NJ, Nanchahal K, Thompson SG, Cuckle HS (1986) Does breathing other people's tobacco smoke cause lung cancer? Br Med J 293:1217–1222

Wells AJ (1986) Misclassification as a factor in passive smoking risk. Lancet 2:638

Wu AH, Henderson BE, Pike MC, Yu MC. Smoking and other risk factors for lung cancer in women. J National Cancer Institute 74:747–751

2023381519

An Introduction to the Study of Smoking Using Urinary Hydroxyproline

H. Kasuga

Summary

The indicators used to identify the effects of environmental tobacco smoke (ETS) and exposure to low level nitrogen dioxide (NO_2) on the respiratory system are so weak that they can not be detected using traditional markers such as the increased prevalence of respiratory symptoms and a decrease in lung function. After studying urinary hydroxyproline (HOP) starting in 1977, we first reported the significant relationship between HOP and smoking, ETS and NO_2 in the air, in 1981. Since then, the coherent association between urinary HOP and the established pathological and biological development of lung diseases has been studied. Bias problems based on confounding factors, misclassification of nonsmokers and over- or underestimation of ETS effects also have been discussed.

Among articles presented by us during the past 4 years, several papers and some arguments for and against this study on urinary HOP were introduced:

1) The effect of cessation from smoking on the urinary excretion of hydroxyproline [19].
2) A prospective repeated cross-sectional study on the possible health effects caused by automobile exhaust and passive smoking [20].
3) Impact of smoking on the concentration and activity of alpha-1-antitripsin in serum, in relation to the urinary excretion of hydroxyproline. Matsuki H, Kasuga H et al., 1988.
4) Behavior of urinary hydroxyproline and effect of cigarette smoking in silicosis. Osaka F, Kasuga H, Matsuki H et al., 1985.
5) Opinions contrary to the relationship between urinary hydroxyproline and smoking, ETS and NO_2.

Introduction

Hydroxyproline (HOP) is one of the essential constituents in collagen and elastine and is an unique one which is not found in other tissues. Therefore, urinary HOP is regarded to be a potential candidate for the study of the breakdown of lung tissue due to smoking and environmental tobacco smoke (ETS).

As is generally known, the index symptom such as "a persistent cough and phlegm" based on the BMRC Questionnaire [1] is used frequently as a clinical marker, but it is not applicable for ETS effects because prevailing concentrations of ETS are estimated to be less than 1% of an undiluted mixture of sidestream and second-hand mainstream smoke. Therefore, urinary HOP as a biochemical marker for ETS effects appeared on the stage, and a causal relationship between smoking including ETS and its health effect was

H. Kasuga (Ed.) Indoor Air Quality
© Springer-Verlag, Berlin Heidelberg 1990

Source: https://www.industrydocuments.ucsf.edu/docs/kznx0000